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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,467	02/14/2006	Mark Louis Heiman	X16339	7932

25885 7590 01/26/2007

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	**PAPER NUMBER**
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	01/26/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 01/26/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/568,467	HEIMAN ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *41-44 and 46-51* is/are allowed.

6)☒ Claim(s) *45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060214*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The examination location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1646, Examiner: Xiaozhen Xie.

The Information Disclosure Statement (IDS) filed 14 February 2006 has been entered in full.

Election/Restrictions

Applicant's election of Group I, claims 41-47, with traverse, in the response received on 24 October 2006, is acknowledged.

The traversal is on the ground(s) that there is no explanation provided as to why the inventions of Group I and II are both "independent and distinct" from one another. Applicant argues that the Restriction Requirement does not meet the requirements of the statue and rule for requiring restriction between these inventions. This is not found persuasive because, as clearly stated in the office action (18 October 2006), according to MPEP § 806.05(h), for inventions that are related as product and process of use, they can be shown to be the distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. In the instant case, the antibodies can be used in a

method of purifying or detecting polypeptide, which is a materially different method from the method of treatment.

However, upon review, the product claims have been found to direct to an allowable subject matter. Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), claims 48-51, directed to the process of using the patentable product and depending from or otherwise including all the limitations of the allowable product claims, i.e., claims 41 and 46, previously withdrawn from consideration as a result of a restriction requirement, are now subject to being rejoined. Claims 48-51 are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Claims 41-51 are pending and under examination.

Specification

The disclosure is objected to because of the following informalities:

The instant application claims the priority of provisional Application Nos: 60/500,496, 60/572,249 and 60/582,111. The first line of the specification should include updated cross-reference to related applications. See 37 CFR 1.78 and MPEP § 201.11.

Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 45 is rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant application describes an anti-Ghrelin monoclonal antibody or antigen-binding portion thereof, wherein: a) the light chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 3 and the heavy chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 12; b) the light chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 4 and the heavy chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 13; c) the light chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 30 and the heavy chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 32; or d) the light chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 31 and the heavy chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 33.

Applicant, however, has not described the genus, i.e., anti-Ghrelin monoclonal antibodies or antigen-binding portion thereof wherein a CDR has 1 or 2 conservative amino acid substitutions or terminal deletions. There is no teaching regarding the relationship of structure to function, such as where and what the changes of the

molecule can lead to the binding specificity and inhibiting activity, and how many amino acid residues can be deleted from a CDR without destroying its function. Thus, the claims encompass a genus of molecules, which vary substantially in composition, and could have very different structural and functional characteristics from the antibody that Applicant has disclosed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making of the claimed product, or any combination thereof. In this case, there is no identification of any particular portion of the structure that can be changed, and how many amino acid residues can be deleted from the terminal on any CDR. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the

encompassed genus of peptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an monoclonal antibody or antigen-binding portion thereof, wherein the light chain variable region comprising a peptide with the sequence of SEQ ID NO: 3, 4, 30 or 31, and the heavy chain variable region comprising a peptide with the sequence of SEQ ID NO: 12, 13, 32, or 33, respectively, but not the full scope of the claimed antibody variants or fragments, is adequately described in the disclosure.

Claim 45 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an anti-Ghrelin monoclonal antibody or antigen-binding portion thereof, a pharmaceutical composition comprising same, and a method of treating obesity or a related disorder in a mammal comprising administering to a patient the pharmaceutical composition, wherein the monoclonal antibody or antigen-binding portion thereof comprises: a) the light chain variable region comprising a

peptide with the sequence shown in SEQ ID NO: 3 and the heavy chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 12; b) the light chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 4 and the heavy chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 13; c) the light chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 30 and the heavy chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 32; or d) the light chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 31 and the heavy chain variable region comprising a peptide with the sequence shown in SEQ ID NO: 33, does not reasonably provide enablement for an anti-Ghrelin monoclonal antibody or antigen-binding portion thereof wherein a CDR has 1 or 2 conservative amino acid substitutions or terminal deletions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claim is broad in that it encompasses antibodies or antigen-binding portion thereof, wherein a CDR has 1 or 2 conservative amino acid substitutions or terminal deletions. The specification discloses an monoclonal antibody or antigen-binding portion thereof, wherein the light chain variable region comprising a peptide with the sequence of SEQ ID NO: 3, 4, 30 or 31, and the heavy chain variable region comprising a peptide with the sequence of SEQ ID NO: 12, 13, 32, or 33, respectively, wherein the antibody or antigen-binding portion thereof is capable of binding to human Ghrelin and antagonizing its activity, and can be used for treating obesity or a related disorder in a

mammal. The specification, however, does not provide any guidance for making or using antibody variants possessing the same properties, i.e., binding specificity and antagonizing activity for human Ghrelin. There is no teaching in the specification as to what structural changes can be made to the molecule without loss of function, or that would destroy the characteristics of the molecule. There is no identification as to where the amino acid substitutions can be made, and how many amino acid residues can be deleted from the terminal of a CDR. Further, it is well known in the art that even minor changes in sequence can result in major changes in function, especially if the minor sequence change occurs within an active site or alters the overall conformation of the protein molecule. For example, Cacia et al. (Biochemistry, 1996, Vol. 35, pp. 1897-1903) teach the effect on antigen binding of an isomerized Asp residue located in the CDRs of a recombinant monoclonal antibody. Cacia et al. found that changing Asp-L32 decreased the relative binding affinity for IgE significantly, whether the mutant residue was an alanine, glutamic acid or the isomerization variants of Asp (including a conservative amino acid replacement) (pp. 1901, see pp. 1901, section "Interaction of E25 variants with IgE", and Table 4). Therefore, without teachings in the specification regarding the structures or data supporting the claims drawn to variants of the antibody, one of ordinary skill in the art would not know how to practice the invention commensurate in scope with the claims.

Due to the large quantity of experimentation necessary to generate the nearly infinite number of monoclonal antibody variants or antigen-binding portion thereof recited in the claim, and screen same for binding specificity and inhibiting activity to

human Ghrelin, and further determining their efficacy in treating obesity or a related disorder in a mammal, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide the activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on antibody structure and function, the breadth of the claims which fails to recite any structural limitations for the variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Additional Reference, Cited as of Pertinent art

Nakazato et al. (Nature, 2001, Vol. 409:194-198) teach that anti-ghrelin immunoglobulin G robustly suppressed feeding.

Zorrilla et al. (PNAS, 2006, Vol. 103(35):13226-231) and Carlson et al. (Mol. Interv., 2006, Vol. 6(5):249-252 teach that active vaccination of mature rats against ghrelin decreases feed efficiency, relative adiposity, and body weight gain.

Zhao et al. (Curr. Opin. Drug Discov. Devel., 2006, Vol. 9(4):509-515) teaches that inhibiting the action of Ghrelin with GHS-R anti-sense oligonucleotides, anti-ghrelin antibodies and peptide antagonists leads to decreased food intake and weight loss in rodents.

Conclusion

CLAIMS 41-44 AND 46-51 ARE ALLOWABLE.

CLAIM 45 IS REJECTED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph. D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph. D.
January 15, 2007

EILEEN B. O'HARA
PRIMARY EXAMINER